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Synthesis of some NH-derivatives of ciprofloxacin as antibacterial and antifungal agents

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Abstract

Five NH-derivatives of ciprofloxacin (**2-6**) have been prepared by acetylation/ benzoylation on ciprofloxacin (**1**) in order to carry out screening for antibacterial activities on some gram-positive and gram-negative bacteria. The antifungal activity of these compounds has also been made against *Candida albicans*. All of the derivatives have shown enhanced activities against Gram-negatives bacteria than parent antibiotic, ciprofloxacin among which compounds **2** and **6** are the most potent agents. Regarding the antifungal activity all of the compounds have shown highest activity than ciprofloxacin. All the compounds have been characterized with spectral analysis.

Introduction

Ciprofloxacin hydrochloride belongs to the second-generation broad-spectrum quinolone antibiotic. It functions by inhibiting DNA gyrase, a type II topoisomerase and topoisomerase IV, enzymes necessary to separate bacterial DNA, thereby inhibiting cell division (Crumplin and Smith, 1976; Wang, 1985).

Ciprofloxacin is used for the treatment of urinary tract infections, prostatitis (Hooper and Wolfson, 1991), shigellosis (Bennish et al., 1992), continuous ambulatory peritoneal dialysis infections (Ludlam et al., 1990), some diabetic foot infection (Peterson et al., 1989), typhoid fever, etc. It shows anti-tumor activity against P388 leukemia (Yamashita et al., 1992).

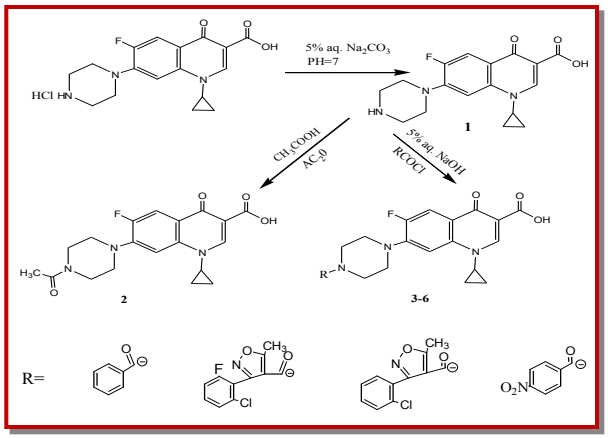
Structure activity relationship, mechanism of action, resistance and clinical aspects of some fluoroquinolones antibacterial have been screened (Goots and Brighty, 1996). A series of benzoquinolizine-2-carboxylic acid arginine salt of nadifloxacin have been synthesized and found out the excellent activity against hospital infections of multi-drug-resistance vancomycin-resistant *Staphylococcus aureus* (de Souza et al., 2005). Effects of skeletal modification of ciprofloxacin on antibacterial, antifungal and cytotoxic activities have been observed and described that some of its derivatives having antifungal properties (Siddiqui et al., 2007). Ciprofloxacin have been incorporated to new series of Schiff base of 1,2,4-triazole via Mannich reaction and got comparable or superior antibacterial results than ciprofloxacin. (Jubie et al., 2010). The pyrazolone derivatives with pyrazole ring extension have been synthesized from ciprofloxacin and observed potential cytotoxicity against brine shrimp neoplasm than ciprofloxacin (Devnath and Islam, 2010).

In recent years the antibiotic resistance is a major concern all over the world in health sector. To find out the desirable antibacterial agent is one of the prime interest of the present scientists. In the light of excellent antibacterial activities of ciprofloxacin and its severe side effect, moreover the antibiotic resistance is a vital issue of present time. We undertook the present study with the aim of substitution the hydrogen of piperazine moiety of the parent molecule with different acyl groups in order to check the influence of newly introduced residue on the antibacterial and antifungal

properties of the ciprofloxacin (Scheme 1).

Materials and Methods

All the synthetic work was done by procuring available laboratory reagents and analytical grade solvents. TLC were performed to monitor the reactions and to determine the purity of the products. Further the compounds were purified by recrystallization using suitable solvents. The melting points of the synthesized compounds were determined in open capillaries using Veego VMP-1 apparatus and expressed in °C and are



Scheme 1

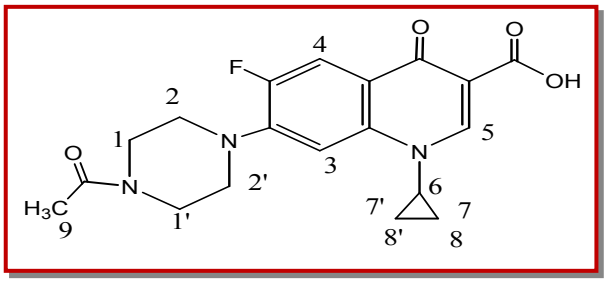
uncorrected. The IR spectrum of compounds was recorded on Shimadzu FT-IR-8400s spectrometer using KBr pellet technique and is expressed in cm^{-1}. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on Bruker DRX-600 (600 MHz FT-NMR) using DMSO, $CDCl_3$ solvents and TMS as internal standard. Mass spectra were obtained using Shimadzu LC-MS (ESI) 2010A spectrophotometer.

Regeneration of free ciprofloxacin and production of ciprofloxacin derivatives: A solution of ciprofloxacin hydrochloride (10 g) in water (50 mL) was treated with an excess of 5% aqueous sodium carbonate solution resulting in the formation of white precipitates which were filtered through suction filter and left to dry as a neutral ciprofloxacin (1, 8.8 g, 88%). These precipitates were pure enough and used as starting material for all the reaction without purification. Ciprofloxacin in acetic acid was reacted with acetic anhydride for derivative (**2**) and ciprofloxacin in 6% aq. NaOH solution was reacted with respective acid chloride to get rest four derivatives (**3-6**).

Synthesis of 7-(4-N-Acetyl-piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1, 4-dihydro-quinoline-3-carboxylic acid (acetylated product, 2): Ciprofloxacin (5 g) was dissolved in acetic acid (40 mL) and then the solution was treated with acetic anhydride (1.6 mL). The reaction mixture was warmed for an hour and allowed to cool for crystallization. The precipitate was filtered off, washed and dried under vacuum in a desiccator. Ciprofloxacin reacted with acetylchloride in presence of THF and TEA, yield 75%).

Product: white crystals (4.5 g); **m.p.=**255°C (decomp.); **Yield** =80%; **HPLC purity**=99%; **Rf value** =0.89. Mobile phase (acetonitrile: concentrated NH_3 solution: CH_3OH:CH_2Cl_2= 10:20:40:40).

IR (cm^{-1}): 3402-2400 (O-H str., H-bonded); 3039(C-H str. aromatic); 2917(C-H str.CH_2); 2853 (C-H str.CH_3); 1720(C=O str., amide); 1628(C=O str., keto acid

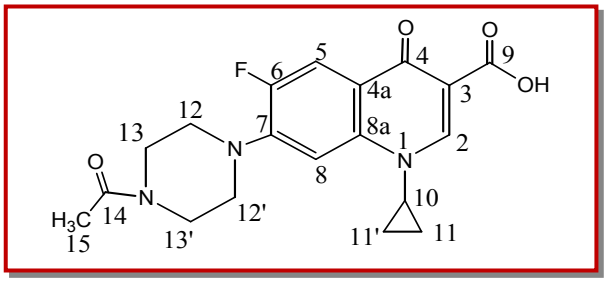


conjugated); 1465 (C-N str.); 1392 (C-O str.); 1300 (C-F str.)

For ^{1}H-NMR

For ^{13}C-NMR

^{1}H-NMR ($CDCl_3$/TMS (600 MHz): $d1_H$



1.22(dd,2H,^{3}J=6.6,4.2 Hz)H-8,8'; 1.41(dd,2H,^{3}J=7.2,6.6 Hz) H-7,7';1.69(s,3H),H-9; 3.30(t,4H ^{3}J=4.2Hz) H-1,1' ; 3.37(t,4H)H-2,2';3.53-3.37(m,1H)H-6;7.37 (d,1H,$^4J_{HF}$=6.6Hz)H-3;8.02(d, 1H $^3J_{HF}$=12.6Hz)H-4; 8.75 (s,1H) H-5.

^{13}C-NMR; $CDCl_3$ (150 MHz): d^{13}_C

9.52(C-11, 11', CH_2 cyclopropyl); 22.56 (C-15 , acetylated CH_3); 36.56 (C-10, CH_2 cyclopropyl); 47.31 (C-13,13', CH_2 piperazine); 51.44 (C-12,12', CH_2, piperazine); 97.35 (C-8); 106.4 (C-3); 109.46 (C-5); 113.9(C-4a); 140.2 (C-8a); 146.67 (C-7); 148.84 (C-2); 154.0 (C-6); 168.09 (C-9, acid group); 170.5 (C-14, amide); 178.3 (C-4, quinolinone C=O).

Elemental analysis: %N = 11.25 calculated; %N = 11.21 found experimentally by Kjeldahl method.

Synthesis of 7-(-4-Benzoyl-piperazin-1-yl)-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid (Benzoylated product, 3): Ciprofloxacin (4 g) was dissolved in 5% NaOH solution and then the solution

was treated with benzoyl chloride (1.5 mL) and the reaction mixture was warmed for an hour and was acidified. White crystal was obtained (Schotten-Baumann method). The precipitate was filtered off, washed and dried under vacuum in a desiccator (ciprofloxacin react with benzoyl chloride in presence of THF and TEA , yield 53%).

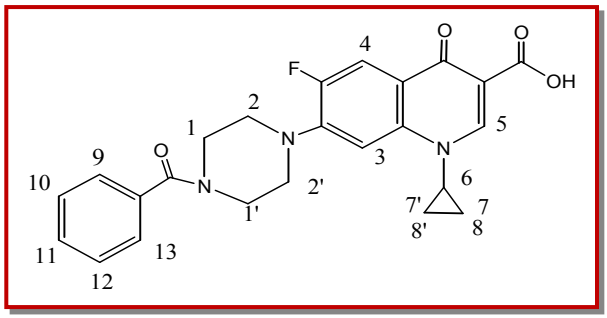
Product: white crystals (4.8); **Yield** =91.60 %; **m.p**.=273-275°C (decomp.); **HPLC purity**=99.85%; **Rf value**= 0.80; Mobile phase (acetonitrile: concentrated NH_3 solution: $CH_3OH:CH_2Cl_2$= 10:20:40:40).

IR (cm^{-1}): 3462-2400 (O-H str, H-bonded); 3102 (C-H str. aromatic); 3057 (C-H str.CH_2); 2862 (C-H str.CH_3); 1722 (C=O acid); 1629 (C=O str. conjugate keto); 1473 (C-N str); 1388(C-O str); 1255(C-F str.).

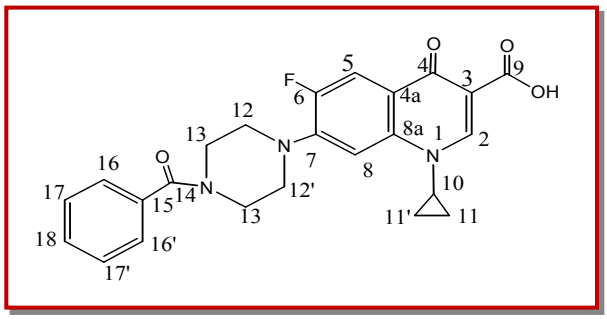
For ^{1}H-NMR

For ^{13}C-NMR

^{1}H-NMR (DMSO-d$_6$/TMS (600 MHz): d^1_H



1.17-1.18 (m,2H) H-8,8';1.32 (t,2H,^{3}J=6.0Hz) H-7,7'; 3.42



(t,4H,^{3}J=16.2Hz) H-1,1'; 3.80 (t,4H) H-2,2'; 3.85 (m,1H) H -6;7.45-7.49 (m,5H) [H-9.10,11,12 and 13] (benzoyl group); 7.6 (d,1H,$^4J_{HF}$=7.2Hz) H-3; 7.93 (d,1H $^3J_{HF}$=13.2Hz) H-4; 8.67 (s, 1H) H-5.

^{13}C-NMR; DMSO-d$_6$ (150 MHz): d$^{13}_C$

10.36 (C-11,11',CH_2 cyclopropyl); 38.67 (C-10,CH_2 cyclopropyl); 48.23 (C-13,13' CH_2 piperazine); 52.39 (C-12,12' CH_2 piperazine); 98.14 (C-8); 109.58 (C-3); 111.27 (C-5); 113.72 (C-4a); 129.83 (C-17,17' meta position benzoyl group); 131.24 (C-16,16'ortho position of benzoyl group); 132.48 (C-18, pera position of benzoyl group); 141.9 (C-8a); 147.80 (C-7); 150.86 (C-2); 154.91 (C -6); 168.67 (C-9, acid group); 171.86 (C-14, amide); 179.14 (C-4, quinolinone C=0).

Elemental analysis: %N=9.65 calculated; %N=9.62 found experimentally by Kjeldahl method.

*Synthesis of 7-[4-{3-(2-choloro-6-fluoro-phenyl)-5-methyl-isooxazole-4-carbonyl}-piperazin-1-yl]-1-cyclopropyl-6-fluoro -4-oxo-1,4-dihydro-quinoline-3-carboxylic acid (**4**):* Ciprofloxacin (3 g) was dissolved in 5% aq. solution of NaOH 25 (mL). Afterwards ethyl acetate solution of FCMIC (2.5 g in 25 mL of ethyl acetate) was added slowly and was stirred the solution for one and half an hours at 10°C. The crystalline product thus deposited. It was filtered off, washed and dried under vacuum in a desiccator.

Product: White crystals (4.25 g); **m.p**.=275-276°C (decomp.); **Yield**=82.64%; **HPLC purity**=99.79%; **Rf value** =0.907; Mobile phase (acetonitrile: concentrated NH_3 solution: $CH_3OH:CH_2Cl_2$= 10:20:40:40).

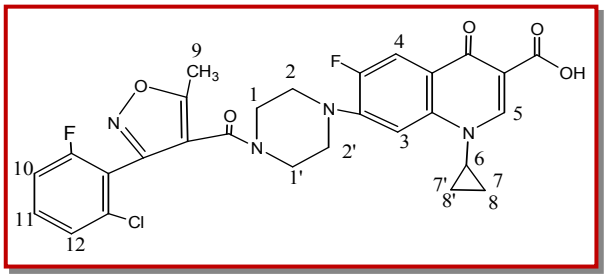
IR (cm^{-1}): 3462-2400 (O-H str. ,H- bonded); 3058 (C-H str., aromatic); 2952 (C-H str.CH_2);1734 (C=O acid); 1627 (C=O str. conjugated keto); 1452 (C-N str); 1392 (C-O str); 1263 (C-F str.).

For ^{1}H-NMR

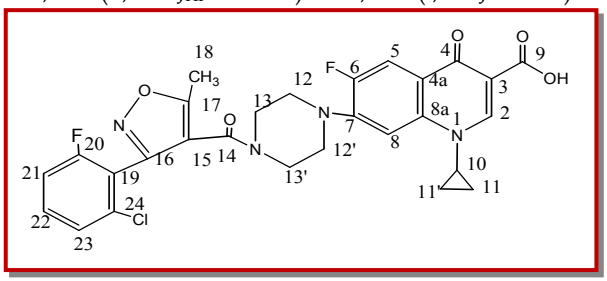
For ^{13}C-NMR

^{1}H-NMR (DMSO-d$_6$/TMS (600 MHz): d^1_H

1.17-1.18 (m,2H)H-8,8'; 1.31(d,2H,^{3}J= 5.4Hz) H-7,7' ;2.90 (s,3H)H-9; 3.24 (t,4H,^{3}J=4.8 Hz)H-1,1'; 3.43(t, 4H,^{3}J=16.2



Hz) H-2,2' ; 3.82(s, broad,1H)H-6; 7.54(d,1H $^4J_{HF}$=7.8Hz) H-3; 7.89(d,1H $^3J_{HF}$=13.2Hz) H-4 ; 8.26(t,1H^{3}J=7.8Hz)H-



11; 8.30(d,1H,^{3}J=8.4 Hz)H-12; 8.38(m,1H)H-10; 8.66(s, 1H)H-5.

^{13}C-NMR; DMSO-d6 (150 MHz): d$^{13}_C$

10.36 (C-11, 11' CH_2 cyclopropyl); 24.10 (C-18, methyl isooxazole); 38.67 (C-10, CH_2 cyclopropyl); l51.24 (C-13, 13', CH_2 piperazine); 52.40 (C-12, 12', CH_2 piperazine); 98.15 (C-8); 100.41 (C-15); 109.58 (C-3); 111.26 (C-5); 113.72 (C-4a); 116.43 (C-21); 129.83 (C-19); 131.24 (C-23);

132.49 (C-22); 135.63 (C-24); 138.32 (C-8a); 141.89 (C-7); 147.80 (C-2); 150.86 (C-17); 154.91 (C-6); 159.05 (C-16); 162.86 (C-20); 168.67 (C-9, acid group); 171.86 (C-14, amide); 179.14 (C-4, quinolinone C=0).

ESI-MS: 569.1102 (M+H)

Elemental analysis: %N = 9.85 calculated; %N = 9.78 found experimentally by Kjeldahl method.

Synthesis of 7-[4-{3-(2-chloro phenyl)-5-methyl-isooxazole-4-carbonyl}-piperazin-1-yl]-1-cyclopropyl-6-fluoro-4-oxo-1, 4-dihydro-quinoline-3-carboxylic acid (5): Ciprofloxacin (3 g) was dissolved in 5% solution of NaOH (25 mL). Afterwards ethyl acetate solution of CMIC (2.31 g in 25 mL of ethyl acetate) was added slowly and was stirred the solution for one and half an hours at 10°C.The crystalline product thus deposited. It was filtered off, washed and dried under vacuum in a desiccator.

Product: white crystals (4.85); **Yield**=81.65%; **m.p**.=268-269°C (decomp.); **HPLC purity**=99.15%; **Rf value** =0.907; Mobile phase (acetonitrile: concentrated NH_3 solution: CH_3OH :CH_2Cl_2= 10:20:40:40).

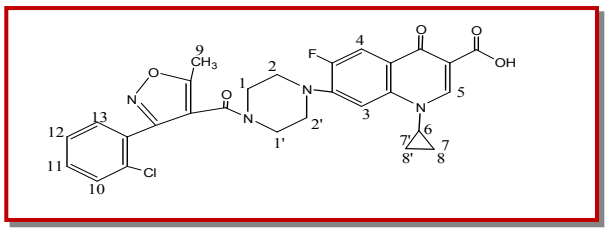
IR(cm^{-1}): 3383-2400 (O-H str.,H-bonded); 3042 (C-H str. aromatic); 1725 (C=O acid); 1624 (C=O str conjugated keto.); 1498 (C-N str.); 1357 (C-O str.); 1298(C-F str.).

For ^{1}H-NMR

For ^{13}C-NMR

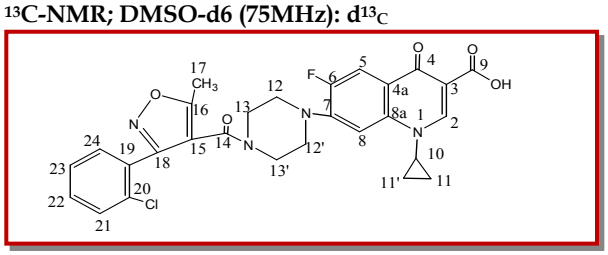
^{1}H-NMR (DMSO-d$_6$/TMS (300 MHz): d^1_H

1.09 (t,2H ^{3}J=7.2Hz) H-8,8' ;1.23 (d,2H,^{3}J= 6.0Hz) H-7,7' ; 2.86 (s,3H) H-9; 3.61 (s br, 4H) H-1,1'; 3.72 (s br,4H)H-2,2'; 3.94 (m, 1H) H-6; 7.38 (d,1H $^4J_{HF}$=6.9Hz) H-3; 7.42-7.56 (m,4H) H-10,11 ,12,13; 7.84 (d,1H, $^3J_{HF}$=12.9Hz) H-4;



8.57 (s,1H) H-5.

^{13}C-NMR; DMSO-d6 (75MHz): d$^{13}_C$



10.32 (C-11, 11', CH_2 cyclopropyl); 23.88(C-17, methyl isooxazole); 38.67 (C-10, CH_2 cyclopropyl); 48.25 (C-13, 13', CH_2 piperazine); 52.39 (C-12, 12', CH_2 piperazine); 98.20 (C-8); 100.90 (C-15); 109.62 (C-3); 111.27 (C-5); 113.70 (C-4a); 120.0 (C-24); 125.92 (C-23); 129.83 (C-21); 131.26 (C-22); 132.45 (C-19); 138.32 (C-8a); 141.89 (C-7); 145.23 (C-18); 147.30 (C-2); 152.06 (C-20); 154.91 (C-6); 159.45 (C-16); 168.67 (C-9, acid group); 171.90 (C-14, amide); 179.15 (C-4, quinolinone C=0).

ESI-MS: 573.1290(M+Na)

Elemental analysis: Found: C 60.78; H 4.14; N 10.21% Calculated: C 61.04; H 4.39; N 10.17%.

Synthesis of 7-[4-(4-nitro-benzoyl)-piperazin-1-yl]-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid (6): Ciprofloxacin (1.8 g) was dissolved in 5% aq. NaOH (25 mL) solution and was added of finely powdered 4-nitro benzoyl chloride and was shocked the mixture vigorously in a stopper test tube. The acid chloride was soon dissolved and was filtered the mass and was acidified and the reaction mixture was warmed for an hour and allowed to cool for crystallization (Schotten-Baumann method). The precipitate was filtered off, washed and dried under vacuum in a desiccator.

Product: white crystals (2.1 g); **Yield** =81.36%; **m.p**.=225 -226^{0}C; **HPLC purity** =99.34%; **Rf value**= 0.65. Mobile phase, (acetonitrile: concentrated NH_3 solution: CH_3OH:CH_2Cl_2= 10:20:40:40).

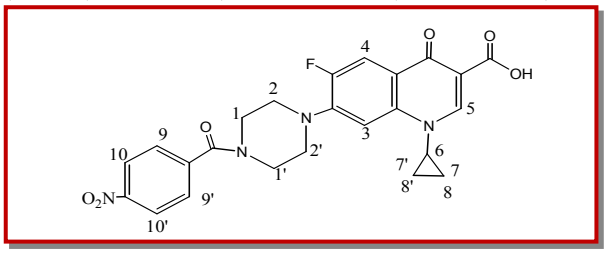
IR(cm^{-1}): 3420-2400 (O-H str., H-bonded); 3055 (C-H str. aromatic); 2922 (C-H str CH_2); 1718 (C=O, acid); 1627 (C=O str. conjugated keto);1490(C-N str.);1338(C-O str.);1267 (C-F str.).

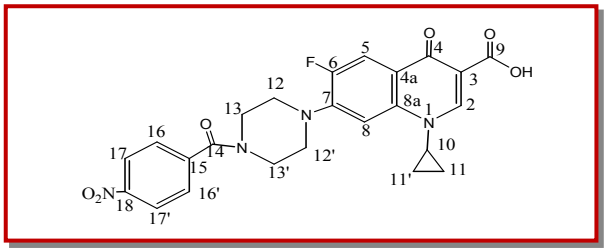
For ^{1}H-NMR

For ^{13}C-NMR

^{1}H-NMR (DMSO-d$_6$/TMS (600 MHz): d^1_H

1.18-1.19 (m, 2H) H-8,8'; 1.31-1.32 (m, 2H) H-7,7'; 3.17 (t,4H,^{3}J=4.2Hz) H-1,1'; 3.43 (t,4H,^{3}J=5.4Hz) H-2,2'; 3.84 (m, 1H) H-6;7.58 (d,1H,$^4J_{HF}$=7.2Hz) H-3; 7.92 (d,1H





$^3J_{HF}$=13.2Hz) H-4; 8.10-8.11 (m,2H) H-9,9'; 8.23-8.24 (m, 2H) H-10,10'; 8.67 (s, 1H) H-5.

Table I

Minimum inhibiting concentration (mm) values against Gram-positive bacteria

Sample name	Dose (µg)	Cipro (1)	2	3	4	5	6
Staphylococcus aureus	100	8	22	6.5	6.5	7.5	24
Streptococci	100	14	17.5	13.5	12	13.8	18.5
Bacillus spp	100	16	22	13.6	13	13.5	20.5

Table II

Minimum inhibiting concentration (mm) values against Gram-negative bacteria

Sample name	Dose (µg)	Cipro (1)	2	3	4	5	6
E. coli	100	12.5	8	10	9.6	8.5	20
Klebsiella pneumoniae	100	31	21	24	23	24	34.5
Pseudomonas spp	100	34	45	25	15	44	42
Salmonella spp	100	38	24	14	11.5	12	39
Salmonella typhi	100	32	35	28	26	27.5	37
Salmonella typhi (para-A)	100	34	34.5	30	27.5	30	38
Salmonella typhi (para-B)	100	33.5	36	29	27.5	31	36.5
Shigalla dysenteriae	100	32	36.5	32.5	31	34	38.5

Table III

Minimum inhibiting concentration (mm) values against *Candida albicans*

Sample name	Dose (µg)	Cipro (1)	2	3	4	5	6
Candida albicans	40	10	25	16	14	14	26

^{13}C-NMR; DMSO-d6 (150MHz): d^{13}C

8.38 (C-11,11', CH_2 cyclopropyl); 36.65 (C-10, CH_2 cyclopropyl); 46.23 (C-13,13',CH_2 piperazine); 49.05 (C-12,12', CH_2 piperazine); 96.15 (C-8); 107.3 (C-3); 107.53 (C-5); 111.73 (C-4a); 123.92 (C-16,16', nitro benzoyl group); 128.01 (C-17,17', nitro benzoyl group); 131.04 (C -15); 139.9 (C-8a); 146.10 (C-7); 148.82 (C-2); 149.54 (C-18, nitro benzoyl group); 154.32 (C-6); 166.64 (C-9, acid group);167.63 (C-14, amide); 177.11 (C-4, quinolinone C=0).

ESI-MS: 503.1095 (M + Na)

Elemental analysis: %N = 11.66 calculated; %N = 11.59 found experimentally by Kjeldahl method.

Antibacterial studies (in vitro): The synthesized compounds were screened for their antimicrobial affects against 3 Gram-positive organisms namely *Staphylococcus aureus, Streptococci* and *Bacillus spp*; and 8 Gram-negative organisms including *E. coli, Klebsiella pneumoniae, Pseudomonas spp, Salmonella spp, Salmonella typhi, Salmonella typhi (Para-A), Salmonella typhi (Para-B)* and *Shigalla dysenteriae*. In the agar well diffusion method wells were drugged in the media with the help of a sterile metallic borer. Two to eight hours old bacterial inoculums containing approximately 104~106 colony forming units (CFU/mL) were spread on the surface in agar with the help of a sterile cotton swab. Recommended concentration of the test sample (4 mg/mL of DMSO) was then added in their respective wells. The plate was incubated immediately at 37°C for 20 hours or later, if necessary. Antibacterial activity was determined by measuring the diameter of zones showing complete inhibition (mm).

Fungicidal bioassay (in vitro): All of the synthesized compounds (**2-6**) were screened for their antifungal affects against *Candida albicans* and compared with parent compound, Ciprofloxacin. Recommended concentration of the test sample (4 mg/mL of DMSO) was then added in their respective wells. The plate was incubated immediately at 37°C for 20 hours or later, if necessary. The results were determined by measuring

the diameter of zones showing complete inhibition (mm).

Results and Discussion

Ciprofloxacin hydrochloride on treatment with excess 5% aqueous NaOH solution afforded neutral ciprofloxacin (88% yield) which on treatment with acetic anhydride get acetylated product **2** with 80% yield. This product was fully characterization with chromatography analysis, spectral analysis such as IR spectrum, ^{1}H-NMR spectrum, ^{13}C-NMR spectrum, LC-MS (ESI) spectrum and elemental analysis. The derivatives **3-6** were obtained by heating neutral ciprofloxacin in 5% aqueous NaOH with respective acid chloride yield of 82-92%. Extensive use of spectral analysis including IR spectrum, ^{1}H-NMR spectrum, ^{13}C-NMR spectrum, LC-MS (ESI) spectrum and elemental analysis data are consistence on the proposed structures.

The results of *in vitro* antibacterial activity are collected in Table I for Gram-positive and Table II for Gram-negative bacteria. The results of in vitro antifungal activity are collected in Table III for *Candida albicans***.**

All of those experiments compared with parent antibiotic, ciprofloxacin then we observed that, two derivatives **2** and **6** showed enhanced activities than ciprofloxacin against gram-positive organisms which we screened such as *Staphylococcus aureus*, *Streptococc*i and *Bacillus spp*. whereas 5 exhibited similar activity against *Staphylococcu*s and 5 and 3 also showed similar activities against *Streptococci.*

Two derivatives 3 and 6 exhibited enhanced activities than ciprofloxacin against all Gram negative organisms which we tested including *E. coli, Klebsiella pneumoniae, Pseudomonas spp, Salmonella spp, Salmonella typhi, Salmonella typhi Para-A, Salmonella typhi Para-B* and *Shigalla dysenteriae* whereas **2** and **5** showed highest activity against *Pseudomonas spp* moreover 2 exhibited better activity against *Salmonella spp, Salmonella typhi, Salmonella typhi Para-A, Salmonella typhi Para-B* and *Shigalla dysenteriae* likewise **3** showed similar activity against *Shigalla dysenteriae.*

In generally, we can say derivative 6 showed enhanced activities than ciprofloxacin against all Gram-positive and Gram-negative organisms likewise **2** and **5** showed highest activity against *Pseudomonas spp* moreover 2 exhibited better activity against *Salmonella spp, Salmonella typhi, Salmonella typhi (Para-A), Salmonella typhi (Para-B)* and *Shigalla dysenteriae* .

All of the synthesized compounds (**2-6**) were screened for their antifungal affects against *Candida albicans* and compared with parent antibiotic, ciprofloxacin. We observed all of the synthesized compounds showed enhanced activities than ciprofloxacin and derivative **6** showed the highest activity.

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